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The Stereoselective Synthesis of α,β-Unsaturated Ketones by the Stepwise Cross-Coupling Reaction of [E]-(2-Bromoethenyl)diisopropoxyborane[1)]

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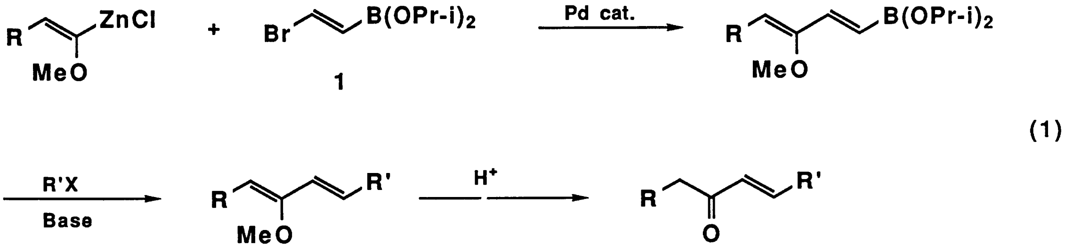
The palladium catalyzed stepwise cross-coupling reaction of (E)-(2-bromoethenyl)diisopropoxyborane, readily available by bromoboration of acetylene, with α-alkoxyalkenylzinc chlorides and organic halides gives α,β-unsaturated ketones in good yields with high (E)-selectivity.

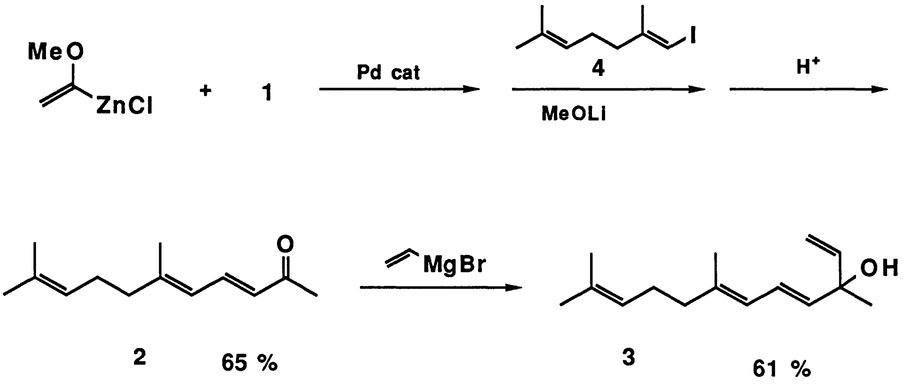
The cross-coupling reaction of α-alkoxyvinylic metal compounds with alkenyl or aryl halide provides a convenient method to introduce acyl functions into alkenyl or aryl group.[2)] However, for the application of such a reaction to the synthesis of complicated α,β-unsaturated ketones or polyenones, the synthesis of starting alkenyl halides having rather complex structure is required and is sometimes tedious. Recently we reported that by using (E)-(2-bromoethenyl)diisopropoxyborane (**1**) as a building block, conjugated polyenes can be synthesized regio- and stereoselectively from simple alkylzinc compounds and alkyl halides.[3)] As the extension of that work, we have investigated the cross-coupling reaction of α-alkoxyalkenylzinc chloride with **1** for a simple and stereoselective synthesis of α,β-unsaturated ketones (Eq. 1).



Methoxyvinylic zinc chlorides were prepared by the addition of $ZnCl_2$ to corresponding lithium compounds[4)] in THF.[5)] The cross-coupling reaction of **1** with methoxyvinylic zinc chlorides was carried out by stirring at room temperature for a few hours in the presence of palladium catalyst. Without isolation of the dienylborane intermediates, base and organic halides were added for the second coupling reaction. As the catalyst used in the first step also worked in the second step, addition of the catalyst was not necessary in the latter step. The resulting dienyl ethers were hydrolyzed by treatment with aqueous HCl without isolation to give expected α,β-unsaturated ketones. In the present method, no isolation of any intermediates is necessary and the desired product can be obtained directly. The representative results for the preparation of α,β-unsaturated ketones are shown in Table 1. Even dienones (Entries 5 and 6 in Table 1) and functionalized dienones (Entries 7 and 8) are also prepared from simple compounds in a similar way as above. As well as methyl ketones, other alkyl ketones were also synthesized. For example, the pentyl ketone was obtained by using 1-methoxy-1-hexenylzinc chloride6) (Entry 9).

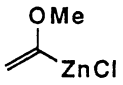
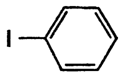
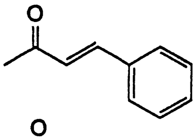
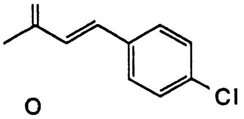
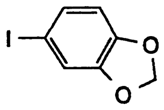
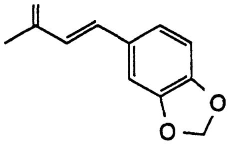
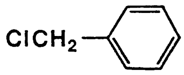
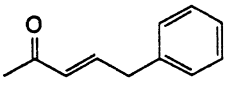
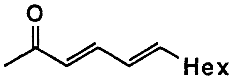
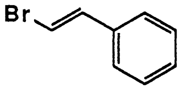
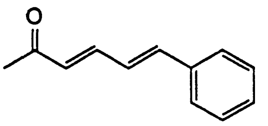
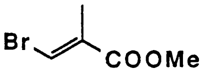
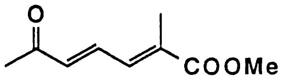
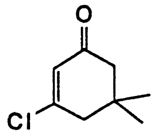
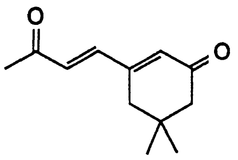
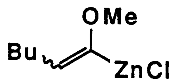
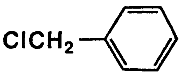
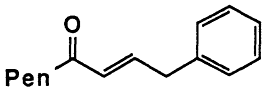
The following procedure for the synthesis of benzalacetone is representative. To 10 mL of a THF solution of methyl vinyl ether (60 ml as gas, ca. 2.4 mmol) was added at -78 °C a pentane solution of t-BuLi (0.74 mL of 2 M solution, 1.5 mmol) to give a pale yellow solution. The cooling bath was removed and the mixture was stirred at room temperature for 10 min. Then a THF solution of $ZnCl_2$ (1.5 mL of 1 M solution, 1.5 mmol) was added and the mixture was stirred at room temperature for 15 min. In another flask, (E)-(2-bromoethenyl)diisopropoxyborane3) (235 mg, 1 mmol), $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol), and THF (3 mL) were placed and a THF solution of methoxyvinylzinc chloride, prepared as above, was introduced at 0 °C through double ended needle. The mixture was stirred at room temperature for 3 h and then an aqueous solution of lithium methoxide (10 mL of 2 M solution, 20 mmol) and iodobenzene (122 mg, 0.6 mmol) were added successively. The reaction mixture was stirred under reflex for 15 h and then treated with aqueous HCl (10 mL of 3 M solution). After stirring for 30 min, the product was extracted with ether and the organic layer was dried over magnesium sulfate. The volatile part was removed under reduced pressure and benzalacetone was obtained in 71% yield by purification using preparative tlc (silica gel, dichloromethane).

In order to demonstrate the utility of our reaction, we attempted to synthesize (±)-4,5-dehydronerolidol (**3**), a constituent of Brickellia lactiniata oil.12) Pseudoionone (**2**) was prepared directly from the dienyl iodide (**4**)9) by the stepwise cross-coupling reaction with **1** and methoxyvinylzinc chloride in 65% overall yield. The stereoisomeric purity of **2** was found to be more than 96%. By the reaction of **2** with vinylmagnesium bromide, the expected dehydronerolidol (**3**) was obtained in 61% yield from **2** (Eq. 2).



(2)

Table 1. The Synthesis of α,β-Unsaturated Ketones[a)]

Entry	Vinylic zinc chloride	Halide	Product[b)]	Yield/%[c)]
1				71
2				87
3				68
4				84[d)]
5				62
6				65
7				74
8				73
9				77[d)]

a) Unless otherwise mentioned, 2.5 equiv. of methoxyvinylic zinc chloride and 1.7 equiv. of **1** to halide were used.

b) Isomeric purity of all products was more than 98%.

c) Isolated yield based on alkyl halide used.

d) In these cases, 1.5 equiv. of methoxyvinylic zinc chloride and 1 equiv. of **1** to benzyl chloride were used.

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2) C. E. Russell and L. S. Hegedus, J. Am. Chem. Soc., 105, 943 (1983).

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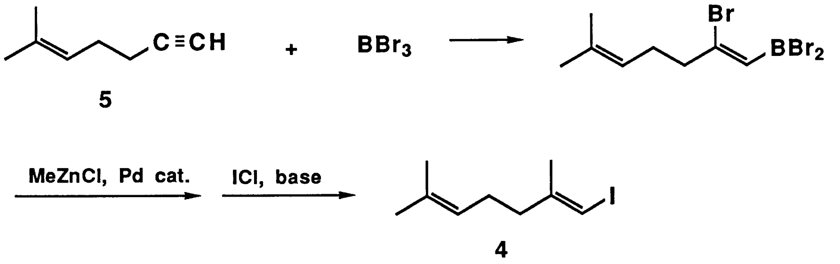
6) This reagent was prepared from the corresponding tin reagent[7] by successive transmetallations. Namely, the tin reagent in THF was treated with BuLi at -78 °C for 1 h, and then with $ZnCl_2$ in THF. The mixture was allowed to warm up to room temperature.

7) The tin derivative was prepared from methyl (E)-1-hexenyl ether[8] by treatment with t-BuLi in hexane-TMEDA at -20 °C, followed by addition of tributyltin chloride. The distillation under reduced pressure gave the desired tin reagent.

8) H. Sugimura and H. Takei, Chem. Lett., 1985, 351.

9) The dienyl iodide (**4**) was prepared from 6-methyl-5-hepten-1-yne (**5**) by the bromoboration reaction, cross-coupling reaction,[10] and iodination[11] sequences.



(3)

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